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taneous recovery is rare (8–11). Idebenone is a synthetic short-chain benzoquinone that bypasses the dysfunctional complex I and restores mitochondrial function, thus increasing ATP production and reducing lipid peroxidation and oxidative stress (12–14).

The first randomized double-blind placebo-controlled trial of idebenone in LHON patients (Rescue of Hereditary Optic Disease Outpatient Study [RHODOS]) demonstrated a trend toward an improved best-corrected visual acuity (BCVA) in the idebenone-treated intent-to-treat population compared with placebo (15). Idebenone (Raxone, idebenone 150 mg tablets, Santhera Pharmaceuticals, Pratteln, Switzerland) is since 2015 the first and currently the only approved treatment (European Medicines Agency (EMA) approval in the European Union and some other countries) for adults and adolescents with LHON.

In 2011, the manufacturer setup an international Expanded Access Program (EAP) to provide special access to idebenone, within local regulations, provided they had a genetically confirmed LHON and disease duration of less than 12 months since the onset of vision loss (most recently affected eye). All requests for access to idebenone were unsolicited, and the manufacturer was not involved in any clinical decision. Here, we describe the EAP patient population and report on clinical outcomes and safety, after ongoing long-term treatment with idebenone in clinical practice.

## METHODS

The idebenone dose and duration of therapy were entirely at the discretion of the treating physician. Patient follow-up was in accordance with routine clinical practice, typically at 3-month intervals.

For each participant, data on visual acuity (VA) and adverse events (AEs) were collected. The BCVA was generally assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) charts with logarithm of the minimal angle of resolution (logMAR) values or converted from standard Snellen notation to logMAR for analysis purposes (16). Efficacy was evaluated by outcome criteria. Clinically relevant stabilization (CRS) of BCVA was defined as a patient having a logMAR of  $<1.0$  at baseline (above the threshold of severe vision loss/legal blindness in the United States (17)) in at least one eye that was maintained in this eye at their last observation visit (LV). A clinically relevant recovery (CRR) of BCVA was defined as an improvement from off-chart (i.e., unable to read any letters on an ETDRS chart from 1 m;  $>1.68$  logMAR) to on-chart by at least one full line (5 letters), or an improvement in an on-chart BCVA by at least 2 lines (10 letters; 0.2 logMAR). The time to initial observation of a CRR was taken as the criterion for an event-based analysis, and the magnitude of recovery is reported as the best recovery observed for

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a patient. Safety and pregnancy information was collected according to the applicable pharmacovigilance (PV) requirements (see **Supplemental Digital Content**, Data E1, <http://links.lww.com/WNO/A407>).

Ethics approval was obtained by the Ethical Committee of the Ludwig-Maximilian University of Munich in accordance with the Declaration of Helsinki.

## RESULTS

At the time of data cut-off (June 2018), 111 patients from 38 sites in 10 countries had received at least one dose of idebenone and were included in the safety population (SP). Of those, all 87 patients, who carried one of the 3 major LHON mtDNA mutations, had a symptom onset within the 12 months previous to the start of treatment and who had baseline data and at least one follow-up visit with BCVA data after baseline were included in the efficacy population (EP). A flowchart of patients qualifying for safety and efficacy populations or nonqualifying is shown in **Supplemental Digital Content**, Figure E1, <http://links.lww.com/WNO/A407>. The mean treatment duration was 25.6 months (2.4–70.4) (Table 1).

Patient demographics were generally representative of the known disease characteristics of LHON. Three patients, all G11778A carriers, reportedly had one eye declared unaffected at baseline, namely, a 14-year-old boy, a 16-year-old boy and a 21-year-old woman.

### Clinically Relevant Stabilization of BCVA

In the EP, 24 of the 87 subjects had a BCVA at baseline better than  $<1.0$  logMAR in at least one eye, 50% (12/24) of whom experienced CRS (Table 1 and 2). For patients with CRS, the mean BCVA improved from 0.47 logMAR at baseline to 0.29 logMAR at the LV.

Of the 3 patients with one unaffected eye at baseline, the 16-year-old patient deteriorated to an off-chart BCVA in both eyes after 6 months of therapy, with no recovery at the LV. However, both the 14-year-old male patient and the 21-year-old female patient still had a normal BCVA at the LV after 12 months' follow-up. These 2 patients also had a CRR in the fellow eye, which had presented with a BCVA worse than 1.0 logMAR at start of treatment.

### Clinically Relevant Recovery of BCVA from Nadir

Of the 87 patients, 40 patients (46.0%) (by eyes, 67/173; 38.7%) had a CRR from nadir to the LV (Table 3). The proportion of eyes with a CRR is lower than the proportion of patients with a CRR because not all patients experienced recovery in both eyes. Time to *initial* observation in patients with a CRR varied between 2.5 and 26.5 months, with a mean of 9.5 months (Fig. 1). The magnitude of recovery of patient's best recovering eye averaged 0.45 logMAR at

*initial* observation of CRR and increased to 0.72 logMAR by the LV. This increase of the magnitude of response with longer treatment duration is confirmed when the magnitude of CRR was analyzed specifically in 22 eyes that had demonstrated a CRR by 6 months and for which follow-up data of 12 month or longer were available (Fig. 2, right). Eyes that eventually achieve a CRR and important VA improvement can, nevertheless, show some degree of transient deterioration into a nadir, despite the start of treatment (Fig. 2, left and **Supplemental Digital Content**, Data E2, <http://links.lww.com/WNO/A408>). Eyes can show a CRR regardless of VA category achieved at nadir. For 173 eyes in 87 patients (one patient's eye had vision loss attributed to another ocular pathology), at nadir 86 (49.7%) were off-chart; 76 (43.9%) had a BCVA 1.0–1.68 logMAR; and 11 (6.4%) had a BCVA below 1.0 logMAR. For eyes that at nadir were off-chart, 24.4% had a CRR, compared with 53.9% from those between 1.0–1.68 logMAR and 45.5% of those better than 1.0 logMAR at nadir (**Supplemental Digital Content**, Data E2, <http://links.lww.com/WNO/A408>).

The overall outcome resulting from the shift of patients across BCVA categories is visualized in Figure 3.

## Safety

The cumulative exposure to idebenone in the SP was 1,981 patient-months. Although patient adherence data are not available, idebenone (150 mg tablets) was prescribed at a daily dose of 900 mg (300 mg three times a day).

In the 111 patients treated with idebenone, 65 AEs (60.7% mild; 4.5% moderate; 4.5% severe) were reported in 32 patients. The most common AEs were gastrointestinal ( $n = 17$ ), with diarrhea the most frequent ( $n = 5$ ). Nine serious AEs were reported in 7 patients (all considered "not related" to treatment). Three cases with a fatal outcome, unrelated to idebenone use, were reported. Nine patients discontinued treatment because of AEs.

## DISCUSSION

The data from this EAP provide unique and novel insights into the efficacy and safety of idebenone treatment in LHON in a real-world setting. Patients with LHON experience rapid vision loss, thus 2 therapeutic goals may be defined depending on the stage of progression. For patients who have suffered a relevant degree of vision loss, the aim is to improve the BCVA as much as possible, at least to a CRR. For patients with relevant residual vision, stabilization of BCVA is important, particularly if 'severe vision loss' has not yet been reached. Achieving either goal, CRR or CRS, may be considered a clinically relevant benefit for patients.

### Clinically Relevant Stabilization

Vision loss in untreated patients is rapid (5), with more than 70% of eyes progressing to a BCVA worse than 1.0

**TABLE 1.** Patient demographics and baseline (BL) values\*. Efficacy population (EP) by mutation†

	All	G11778A	G3460A	T14484C
Patients in the EP	87/87 (100%)	54/87 (62.1%)	17/87 (19.5%)	16/87 (18.4%)
Treatment duration (mo)‡	25.6 ± 16.9 (2.4–70.4)	24.9 ± 17.4 (3.2–70.4)	27.7 ± 16.7 (4.4–61.0)	25.5 ± 16.0 (2.4–53.8)
Gender male	71/87 (82%)	45/54 (83%)	13/17 (77%)	13/16 (81%)
Age at onset (y)	31.4 ± 17.3 (6.6–78.9)	33.3 ± 17.5 (12.1–78.9)	28.4 ± 16.8 (6.6–64.5)	28.1 ± 16.9 (8.5–56.2)
Adolescent at onset (age 12–17 y)	22/87 (25.3%)	11/54 (20.4%)	6/17 (35.3%)	5/16 (31.3%)
Childhood onset (<12 y of age)	3/87 (3.4%)	0/54 (0%)	1/17 (5.9%)	2/16 (12.5%)
Time since onset at baseline   (mo)	4.6 ± 3.0 (0.3–11.5)	4.3 ± 2.7 (0.4–11.4)	5.9 ± 3.7 (0.3–11.5)	4.4 ± 2.8 (0.9–9.3)
Interval of onset between eyes¶# (mo)	1.7 ± 2.5 (0.0–12.6)	1.8 ± 2.5 (0.0–10.0)	1.9 ± 3.1 (0.0–12.6)	0.9 ± 1.3 (0.0–4.7)
BCVA at baseline [logMAR]§	1.23 ± 0.52 (–0.18–1.8)	1.22 ± 0.59 (–0.18–1.8)	1.37 ± 0.38 (0.40–1.80)	1.12 ± 0.39 (0.28–1.80)
Baseline BCVA off-chart**	17/87 (20%)	13/54 (24%)	3/17 (18%)	1/16 (6%)
Baseline BCVA from 1.0 to 1.68 logMAR	46/87 (53%)	25/54 (46%)	11/17 (65%)	10/16 (63%)
Baseline BCVA <1.0 logMAR	24/87 (28%)	16/54 (30%)	3/17 (18%)	5/16 (31%)

Values are given as n (%) or mean ± SD and minimum–maximum (in parentheses); percentages may not total to 100% due to rounding.

\*Data cut-off: June 2018.

†For information on EP flow see **Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A407>.

‡Treatment duration was not predetermined and was decided by the treating physician according to his/her criteria as per routine clinical practice.

§BCVA off-chart values are imputed to 1.8 logMAR see **Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A407>.

||Time since onset: time from symptoms onset to start of treatment (baseline) in the most recently affected eye.

¶Three patients were reported by the treating physician to have one asymptomatic eye at baseline.

#Time between onset of first and second affected eye.

\*\*Off-chart values: not reading any letter on the ETDRS chart at 1 m (i.e., >1.68 logMAR) (**Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A407>).

BCVA, best-corrected visual acuity; CRS, clinically relevant recovery; CRS, clinically relevant stabilization; logMAR, logarithm of the minimal angle of resolution; mo, months; y, years.

**TABLE 2.** Clinically relevant stabilization (CRS) for the subset of patients with a BCVA at baseline <1.0 logMAR. Efficacy population (EP)\*† by mutation

	All	G11778A	G3460A	T14484C
BCVA stabilization: Patients with CRS‡	12/24 (50%)	7/16 (44%)	1/3 (33%)	4/5 (80%)
BCVA at baseline [logMAR]	0.47 ± 0.36 (–0.18–0.96)	0.31 ± 0.34 (0.18–0.88)	0.94	0.62 ± 0.28 (0.28–0.96)
BCVA at last observation [logMAR]	0.29 ± 0.29 (–0.16–0.8)	0.35 ± 0.34 (–0.16–0.8)	0.34	0.17 ± 0.29 (–0.14–0.42)
Treatment duration [months]§	30.1 ± 19 (9.9–67.8)	25.5 ± 20.6 (10.7–67.8)	40.0	35.8 ± 18.6 (9.9–53.8)

Values are given as n (%) or mean ± SD and minimum–maximum (in parentheses); Percentages may not total to 100% due to rounding.

\*Data cut-off: June 2018.

†For information on EP flow see **Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A409>.

‡CRS: BCVA had to be maintained in an eye with BCVA <1.0 logMAR at start of the treatment.

§Calculations only consider patients with CRS (12 patients).

BCVA, best-corrected visual acuity; CRS, clinically relevant stabilization; logMAR, logarithm of the minimal angle of resolution.

**TABLE 3.** Clinically relevant recovery (CRR) by patient. Efficacy population (EP)\*† by mutation

	All	G11778A		G3460A		T14484C		
BCVA recovery: Patients with a CRR †	40/87 (46.0%)	21/54 (39%)		7/17 (41%)		12/16 (75%)		
Time to an initial CRR [months]	9.5 ± 7.0 (2.5–26.5)	11.2 ± 7.8 (2.5–26.5)	7.3 ± 3.4 (2.5–12.9)	7.8 ± 6.8 (3.0–25.6)				
Magnitude of recovery at initial CRR								
logMAR	0.45 ± 0.31	0.20–1.62	0.39 ± 0.32	0.20–1.62	0.39 ± 0.20	0.22–0.76	0.60 ± 0.30	0.22–1.20
No. of letters ETDRS	22 ± 15 (10–81)		19 ± 16 (10–81)		19 ± 10 (11–38)		30 ± 15 (11–60)	
Magnitude of recovery at last observation								
logMAR	0.72 ± 0.46	0.20–1.80	0.52 ± 0.39	0.20–1.76	0.61 ± 0.31	0.24–1.10	1.12 ± 0.40	0.46–1.80
No. of letters ETDRS	36 ± 23 (10–90)		26 ± 19 (10–88)		30 ± 15 (12–55)		56 ± 20 (23–90)	

Values are given as n (%) or mean  $\pm$  SD and minimum–maximum (in parentheses); percentages may not total to 100% due to rounding.

\*Data cut-off June 2018.

<sup>†</sup>For information on EP flow see **Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A407>.

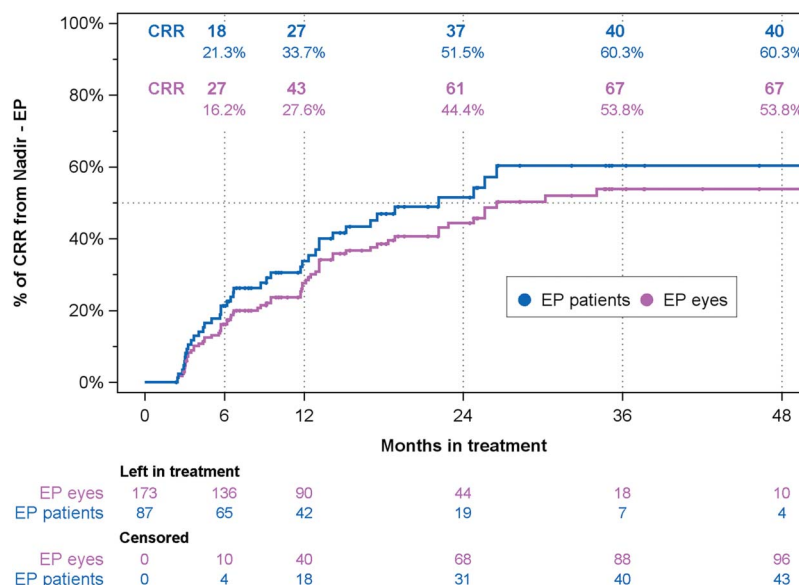
<sup>a</sup>CRR is improvement from an off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (5 letters) or an improvement in an on-chart BCVA by the equivalent of at least 2 lines (10 letters).

BCVA, best-corrected visual acuity; CRR, clinically relevant recovery; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimal angle of resolution.

logMAR (20/200 Snellen) within 3 months (4,18). Accordingly, only 27.6% patients had a BCVA better than 1.0 logMAR at baseline (mean 4.6 months after a symptom onset) (Table 1). Although it is to be expected that most patients would further progress if untreated, with treatment, half of them (12/24, 50.0%) maintained a BCVA below this threshold after an average follow-up time of 24.3 months. One key limitation of CRS is that it does not take into account the fact that the BCVA could still have deteriorated significantly, but not enough to cross the 1.0 logMAR threshold, so it would still qualify as CRS

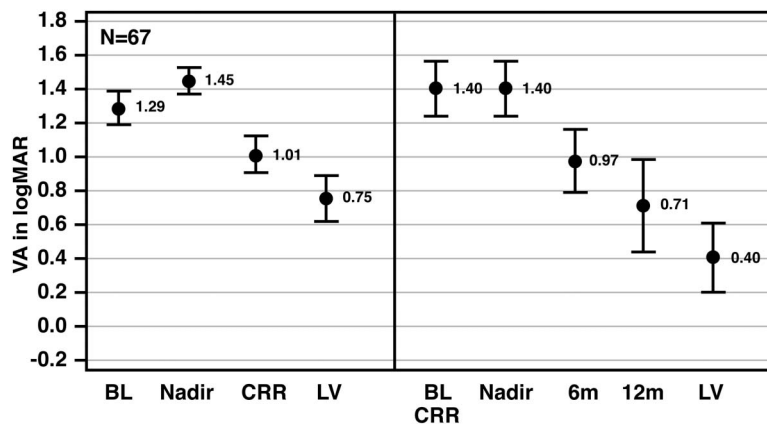
despite having deteriorated. Interestingly, the mean BCVA for these patients improved from 0.47 to 0.29 logMAR, corresponding to 9 letters on the ETDRS chart. Compared with the natural disease course, early idebenone treatment provides an opportunity to prevent severe vision loss over a timespan when further BCVA deterioration would be expected for most patients (19).

In most cases, the journey to LHON diagnosis after a symptom onset takes weeks or months, usually not allowing for treatment initiation until the second eye becomes affected. Notably, in the EAP, only 3 patients

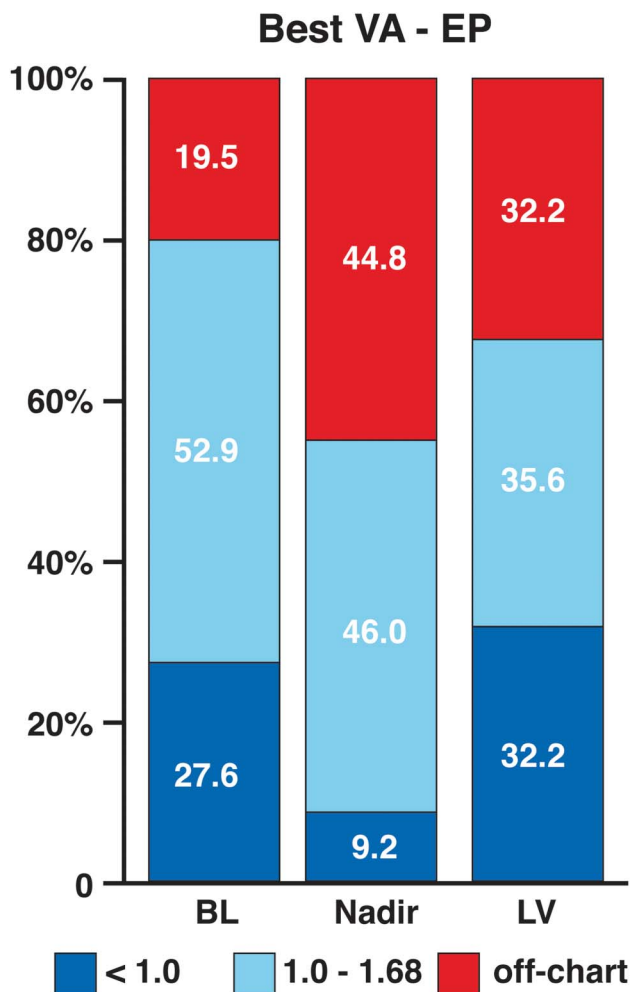


**FIG. 1.** Kaplan–Meier curves of clinically relevant recovery (CRR). Cumulative percentage of total number of patients and eyes, respectively, with a CRR, as a function of treatment duration, in the efficacy population (EP).





**FIG. 2.** Magnitude of mean BCVA recovery over the course of time in eyes with a CRR. Magnitude of best-corrected visual acuity (BCVA) recovery in eyes with a clinically relevant recovery (CRR). Left: Average BCVA observed at baseline (BL), nadir, initial observation of CRR, and at the last observation visit (LV) for all eyes that experienced a CRR ( $n = 67$ ). Right: Improvement of BCVA over the course of time, at given treatment durations, in those eyes that experienced a CRR within 6 months of treatment initiation and where follow-up data were available ( $n = 22$ ). All mutations. All off-chart VA values were imputed to 1.8 logMAR. Error bars indicate the 95% CI.



**FIG. 3.** Shift of patients, over the course of treatment time, across categories of BCVA (efficacy population,  $n = 87$ ). Bar chart for distribution of patients based on categories for the best-corrected visual acuity (BCVA) at baseline (BL), at nadir, and at the last observation visit (LV) mutations. EP, efficacy population.

had one unaffected eye at the start of treatment, 2 of which maintained this status at the LV. Although the numbers are low, this contrasts with a previous case series, in which all 6 patients starting idebenone treatment with an unaffected eye subsequently experienced a BCVA decrease in these eyes (8). Although this is a good indication of a favorable effect, the small numbers mean it remains to be seen whether idebenone can indeed prevent the onset of symptoms, that is, in patients starting treatment “in-between” onset in the eyes. This can be further explored once better referral and earlier diagnosis result in widespread early treatment of the disease.

#### Clinically Relevant Recovery

Vision loss in patients with LHON is mostly permanent (19). However, in the EAP, almost one in 2 patients (40/87, 46.0%) treated with idebenone experienced a CRR after a mean treatment duration of 9.48 months. This is comparable with the 45.5% (20/44) responder rate for idebenone-treated patients in a case series using similar criteria to define recovery (8), and of 42.9% (6/14) reported for a smaller patient cohort treated with idebenone and vitamin B2 (9). Both of these retrospective studies reported lower rates of recovery, 32.2% (8) and 28.6% (9), for the untreated, in-study control groups. Although the EAP did not have a control group, a recently conducted, large retrospective case record survey provided rates of CRR using identical criteria as in the EAP (20,21). In this study, 31.1% of untreated patients (23/74) experienced a CRR, a proportion again in line with the untreated groups of the 2 cohort studies (8,9).

#### Rate of Recovery as a Function of Treatment Duration

This EAP provides a large data set in patients treated for an average of more than 2 years (in RHODOS was 6 months).

**TABLE 4.** Clinically relevant recovery (CRR) by individual eyes as a function of BCVA at nadir. Efficacy population (EP)\*†

VA Category at Nadir	Eyes	Eyes With a CRR‡ Within Category	Eyes With a CRR and BCVA [logMAR] at the Last Observation		
			BCVA > 1.0	>0.5 BCVA <1.0	BCVA ≤ 0.5
Off-chart	86/173 (49.7%)	21/86 (24%)	14	2	5
From 1.0 to 1.68 logMAR	76/173 (44%)	41/76 (54%)	12	13	16
Below 1.0 logMAR	11/173 (6%)	5/11 (46%)	na	0	5
All§	173/173 (100%)	67/173 (39%)	26	15	26

Values are given as n (%); Percentages may not total to 100% due to rounding.

\*Data cut-off June 2018.

†For information on EP flow see **Supplemental Digital Content**, Supplemental Data A, <http://links.lww.com/WNO/A407>.

‡CRR is improvement from an off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (5 letters) or an improvement in an on-chart BCVA by the equivalent of at least 2 lines (10 letters) at LV.

§One patient had vision loss in one eye not related to LHON.

BCVA, best-corrected visual acuity; CRR, clinically relevant recovery; logMAR, logarithm of the minimal angle of resolution; na, not applicable.

In the EAP, time from start of therapy to initial observation of CRR varies from 2.5 to 26.5 months (Table 3). This provides evidence for a benefit of longer idebenone treatment in LHON because only 45.0% of the total responders had experienced their first recovery by 6 months. The responder rate increased with treatment duration up to 12 months, but 33% patients experienced a CRR later, with some only showing initial improvement after 24 months of treatment (Fig. 1).

### Magnitude of Recovery as a Function of Treatment Duration

Evaluating the impact of continued therapy *after an initial CRR has been observed* is very relevant. At the initial CRR, the average magnitude of best recovery by subject was 23 letters, which increased to 36 letters (7 lines ETDRS) by the LV. This effect was also observed for individual eyes with a CRR (n = 67) where after first worsening to a nadir, later improved at initial observation of CRR and further at the LV (mean recovery of 35 letters from nadir) (Fig. 2, left). Finally, in a subset of eyes demonstrating an early CRR (within 6 months), the magnitude of CRR continued to increase with prolonged treatment, from 21 letters after 6 months to 50 letters by the LV (average treatment duration of 35 months).

### Rate of Recovery and Outcome as a Function of Vision Loss During Therapy

An interesting question to address is whether the results of therapy are dependent on the degree of BCVA loss, both in terms of responder rate and to a change in categorical BCVA outcomes, as defined by BCVA thresholds related to quality of life (17). At the start of treatment, 27.6% patients presented with a BCVA <1.0 logMAR and 19.5% were already off-chart, highlighting the rapid vision loss described elsewhere (11,19,22). Visual outcomes showed some further worsening after treatment initiation, reaching a nadir.

At the final available assessment, however, visual outcomes were markedly improved compared to nadir, with more than a tripling of patients with a BCVA <1.0 logMAR from nadir (9.2%) to the LV (32.2%) and a reduction in off-chart patients (44.8%–32.2%) (Fig. 3). Although a CRR can be achieved both in on-chart and off-chart eyes, the proportion of CRR was higher for eyes being on-chart at nadir (53.9%) than for eyes being off-chart at nadir (24.4%) (Table 4 and **Supplemental Digital Content**, Data E2, <http://links.lww.com/WNO/A408>).

Also, for responders, the magnitude of improvement can be very marked, regardless of the severity at nadir.

### Impact of Leber Hereditary Optic Neuropathy Mutation on the Reported Analyses

The most frequent mitochondrial gene variant causing LHON, G11778A, is considered to correlate with the most severe prognosis, whereas the T14484C mutation is typically associated with a milder phenotype, and the G3460A mutation has an intermediate prognosis (2,10,22). The largest subgroup of patients in the EAP were G11778A. They experienced a slightly lower rate of CRS than the entire cohort, a lower rate of CRR, a smaller magnitude of recovery by the LV, and longer treatment duration to recovery. As expected, although with a small number of patients, T14484C patients had the highest rate of CRS and CRR, the largest magnitude of recovery, and the shortest treatment duration before a CRR, whereas the corresponding rates for patients with the G3460A mutation mostly fell in between the other 2 mutations (Tables 1–3).

With the obvious limitations resulting from varying observation duration and definitions of treatment response (10,15,23–27), rates of spontaneous recovery of VA have been documented in several studies and can be as low as 4% for the G11778A mutation (23–27). In the RHODOS placebo group, spontaneous recovery across all mutations



occurred in 10.3% of patients over 6 months (15). Overall, the CRR rate observed in our data exceeds the reported rates of spontaneous recovery.

Idebenone was well tolerated, with a good safety profile, in line with results from the RHODOS trial (15). No new safety signals have been observed.

Although our analysis has the inherent limitations from the retrospective nature of the data and a lack of control group, it provides, however, an important view of long-term response and tolerability of idebenone in patients within the first year of disease onset in the second eye in a real-world setting.

## CONCLUSIONS

Our results suggest that the overall outcome of idebenone treatment indicates a better long-term prognosis than expected from limited natural history data. Although treatment response is observed despite severity of visual impairment, early treatment initiation improves the chances of response.

A treatment duration of at least 18–24 months is needed to maximize the probability of CRR because a certain degree of transient deterioration to a nadir may occur despite therapy initiation and continued treatment after an initial CRR provides further benefit. The risk balance of idebenone 900 mg/day is in line with the previously published randomized placebo-controlled clinical trial.

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